Short Communication

Merkel Cell Carcinoma and Multiple Primary Cancers

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Abstract

Merkel cell carcinoma (MCC) is an aggressive neuroendocrine tumor of the skin for which causative factors remain largely unknown. The site-specific risks of multiple primary cancers associated with MCC, which may provide insight into etiologic influences, have not been quantified in large population-based studies. We estimated the long-term risk of subsequent primary tumors after a first primary MCC (1,306 patients) and the risk of second primary MCC following other first primary cancers (2,048,739 patients) within 11 population-based cancer registries which report to the National Cancer Institute's Surveillance, Epidemiology, and End Results Program (1986-2002). Patients with first primary MCC were at significantly increased risk of developing a subsequent cancer [standardized incidence ratio (SIR), 1.22; 95% confidence intervals (95% CI), 1.01-1.45; observed (O = 122)], with significant excesses restricted to the first year after diagnosis (SIR, 1.71; 95% CI, 1.21-2.33; O = 39). Significantly elevated site-specific risks were observed for cancers of salivary gland (SIR, 11.55; 95% CI, 2.32-33.76; O = 3), biliary sites other than liver and gallbladder (SIR, 7.24; 95% CI, 1.46-21.16; O = 3), and non–Hodgkin lymphoma (SIR, 2.56; 95% CI, 1.23-4.71; O = 10). Nonsignificantly increased risks of 2-fold or higher were seen for chronic lymphocytic leukemia, and cancers of the small intestine and brain. A significantly increased 1.36-fold risk (95% CI, 1.19-1.55; O = 221) of MCC as a second primary malignancy was observed among patients with all other first primary cancers taken together. In particular, significant 3- to 7-fold excesses of MCC followed multiple myeloma (SIR, 3.70; 95% CI, 1.01-9.47; O = 4), chronic lymphocytic leukemia (SIR, 6.89; 95% CI, 3.77-11.57; O = 14), non–Hodgkin lymphoma (SIR, 3.37; 95% CI, 1.93-5.47; O = 16), and malignant melanoma (SIR, 3.05; 95% CI, 1.74-4.95; O = 16). Although enhanced medical surveillance may play a role, increased reciprocal risks suggest that MCC may share etiologic influences with other malignancies. Heightened awareness of the associations of lymphohematopoietic malignancies with MCC may facilitate early clinical recognition. (Cancer Epidemiol Biomarkers Prev 2006;15(8):1545–9)

Introduction

The etiology of Merkel cell carcinoma (MCC), a rare and aggressive neuroendocrine neoplasm of the skin, is largely unknown (1). MCC occurs most frequently in the elderly and is characterized by a high incidence of local recurrence, metastatic spread, and low survival rates (1). MCC has been reported in association with sun exposure (2), immunosuppression in solid organ transplant recipients (3), and in patients with AIDS (4). Immunologic mechanisms are likely operant because case reports link MCC with chronic lymphocytic leukemia (CLL) and non–Hodgkin lymphoma (1). Both immunosuppression and sun exposure have been cited in the increased risk of MCC after malignant melanoma (2). Few studies, however, have had sufficient numbers to quantify site-specific associations with other cancers; furthermore, bidirectional analyses of risk may provide insight into MCC etiology. Thus, we quantified the site-specific risk of tumors occurring after first primary MCC and the risk of MCC occurring after other first primary tumors in a population-based study of >2 million cancer patients.

Materials and Methods

Patients with a first primary cutaneous MCC or other first primary cancer were identified in 1 of 11 population-based cancer registries of the Surveillance, Epidemiology, and End Results (SEER) Program (1986-2002).[4] The histology code for MCC was first registered by the SEER Program in 1986. Patients with a first primary cutaneous MCC (n = 1,306) and patients with other first primary neoplasms (n = 2,048,739) were evaluated for subsequent cancer risk. Registry incidence files were searched for invasive primary neoplasms that developed at least 1 month prior to or after a diagnosis of MCC. Cancers occurring within 1 month of MCC were excluded from the analysis. Shorter latency periods are typically used to investigate possible common exposures associated with the first primary cancer as opposed to treatment effects that require longer latency periods. The 1 month latency period was chosen to focus on metachronous cancers. Third primary cancers observed in five patients were included in risk calculations. Secondary MCC following primary MCC were excluded from the analysis. One patient experienced two primary MCCs following a first primary kidney cancer, which are included in the risk estimates. Participating registries record initial therapy, which we categorized as surgery alone, any radiotherapy or chemotherapy, other, or unspecified. Treatment for MCC usually consists of wide local excision, with adjuvant radiotherapy administered

Received 11/28/05; revised 5/17/06; accepted 5/31/06.

Contract support: Intramural Research Program of the NIH, National Cancer Institute, Division of Cancer Epidemiology and Genetics.

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doi:10.1158/1055-9965.EPI-05-0895

[4] SEER Program areas include Atlanta (1975+), Connecticut, Detroit, Hawaii, Iowa, New Mexico, San Francisco-Oakland, Seattle-Puget Sound (1974+), Utah, Los Angeles (1992+), and San Jose-Monterey (1992+).

to selected patients (5). When given, chemotherapy typically consists of cyclophosphamide, doxorubicin, and vincristine, or cisplatin and etoposide, although there is no consensus on the optimal regimen (6).

Subsequent cancer risk was estimated by compiling person-years of observation beginning 1 month after cancer diagnosis until the date of death, date of last follow-up evaluation, or end of study (December 31, 2002), whichever occurred first. Patients were not withdrawn from follow-up at the date of diagnosis of a second cancer; therefore, the analysis allowed for risk estimation of third or higher order cancers. SEER Program incidence rates specific for age, sex, 5-year calendar-year periods, and cancer site were multiplied by the accumulated person-years at risk to estimate the number of expected cancers. Reference rates included subsequent primary cancers in the numerator. The total numbers of observed and expected cancers were then summed, and expressed as the ratio of observed-to-expected cases (standardized incidence rate, SIR). Using approximate methods, 95% confidence intervals (CI) were calculated; exact methods were used for sites in which five or fewer cases were observed (7). Findings were considered significant for two-sided $P < 0.05$.

Results

A total of 1,306 patients (746 males and 560 females) was diagnosed with a first primary MCC (Table 1). Patients were followed for a mean of 3.5 years (total person-years, 4,627). One hundred and twenty-two patients developed a subsequent cancer following MCC (SIR, 1.22; 95% CI, 1.01-1.45); overall risk was similar for males [SIR, 1.17; 95% CI, 0.92-1.46; observe (O = 76)] and females (SIR, 1.31; 95% CI, 0.96-1.74; O = 46). Excesses of brain cancer, however, were restricted to males (SIR, 5.45; 95% CI, 1.12-15.93; O = 3), with no cases observed in females. Subsequent cancer risk did not differ among MCC patients treated with surgery only (SIR, 1.27; 95% CI, 0.98-1.62; O = 64), any radiotherapy (SIR, 1.15; 95% CI, 0.85-1.51; O=49), or those whose treatment was designated as chemotherapy, other, or unspecified (SIR, 1.24; 95% CI, 0.57-2.35; O = 9). Among all MCC patients, significantly increased risks (SIR, 1.71; 95% CI, 1.21-2.33; O = 39) of subsequent cancers were restricted to the first year after diagnosis, with 6% to 8% excesses in the 1- to 4-year, 5- to 9-year, and +10-year intervals. The early excesses were due largely to a significantly increased risk of lymphohematopoietic cancers (SIR, 3.77; 95% CI, 1.51-7.77; O = 7), although risks for all solid tumors taken together were nonsignificantly increased (SIR, 1.48; 95% CI, 0.99-2.11; O = 30). The SIR for all subsequent primary cancers was 1.37 (95% CI, 1.05-1.76; O = 62) for patients diagnosed with MCC between 1995 and 2002, and 1.09 (95% CI, 0.83-1.40; O = 60) for those diagnosed in earlier calendar years, but the difference was not statistically significant. For each era, elevated risks of subsequent cancers were restricted to the first year after MCC diagnosis [(1986-1994: SIR, 1.77; 95% CI, 0.99-2.92; O = 15) and (1995-2002: SIR, 1.67; 95% CI, 1.07-2.49; O = 24)].

Following MCC, significantly increased risks were observed for cancers of the salivary gland (SIR, 11.55; 95% CI, 2.32-33.76;

Table 1. Description of 1,306 patients diagnosed with first primary MCC in 11 population-based cancer registries in the SEER Program (1986-2002)

Characteristic	No. of patients (%)	Person-years of follow-up	No. of subsequent primary cancers*	SIR (95% CI)
All patients	1,306 (100)	4,627	122	1.22 (1.01-1.45)†
Male	746 (57.1)	2,520	76	1.17 (0.92-1.46)
Female	560 (42.9)	2,107	46	1.31 (0.96-1.74)
Age at MCC diagnosis				
<60	172 (13.2)	851	11	1.47 (0.73-2.62)
60-69	246 (18.8)	1,200	29	1.14 (0.76-1.63)
70+	888 (68.0)	2,576	82	1.22 (0.97-1.51)
Calendar year of MCC diagnosis				
1986-1994	474 (36.3)	2,601	60	1.09 (0.83-1.40)
1995-2002	832 (63.7)	2,025	62	1.37 (1.05-1.76)†
Anatomic site				
Head	581 (44.5)	1,931	48	1.10 (0.81-1.46)
Trunk	156 (11.9)	511	16	1.44 (0.82-2.34)
Upper limb	273 (20.9)	1,122	26	1.05 (0.68-1.53)
Lower limb	215 (16.5)	832	21	1.29 (0.80-1.97)
Other or unknown‡	81 (6.2)	231	11	2.40 (1.20-4.29)†
Stage				
Localized	636 (48.7)	2,450	60	1.13 (0.86-1.46)
Regional	375 (28.7)	1,243	33	1.25 (0.86-1.75)
Distant	92 (7.0)	163	4	1.05 (0.28-2.68)
Unstaged	203 (15.5)	772	25	1.46 (0.94-2.15)
Initial treatment for MCC				
Surgery only	599 (45.9)	2,229	64	1.27 (0.98-1.62)
Any radiotherapy§	549 (42.0)	2,039	49	1.15 (0.85-1.51)
Chemotherapy/other/unspecified‖	158 (12.1)	359	9	1.24 (0.57-2.35)
Number of patients entering follow-up interval				
<1 year	1,306 (100)	1,035	39	1.71 (1.21-2.33)†
1-4 years	976 (74.7)	2,335	55	1.08 (0.81-1.40)
5-9 years	351 (26.9)	1,022	23	1.06 (0.67-1.59)
10+ years	105 (8.0)	235	5	1.07 (0.34-2.50)

NOTE: All patients were diagnosed and reported to the SEER Program with a histologically confirmed first primary MCC of the skin (January 1, 1986-December 31, 2002). MCC was defined using the International Classification of Diseases for Oncology version 3 morphology code 8247 (21). Due to rounding, percentages in the table may not sum to totals.

*Numbers exclude MCC.

†$P < 0.05$.

‡Includes tumors that overlap the boundaries of two or more subcategories or tumors in which the site of origin is unknown.

§Numbers include patients receiving radiotherapy only (414 patients, 36 subsequent cancers) and those given radiotherapy and chemotherapy (135 patients, 13 subsequent cancers).

‖Numbers include patients receiving chemotherapy only (82 patients, seven subsequent cancers) and those given other or unspecified treatment (76 patients, two subsequent cancers).

Table 2. Site-specific risk of cancers following a first primary MCC in the SEER Program (1986-2002)

Site of subsequent cancer	All subsequent cancers			Cancers occurring after 1 year*	
	No.	SIR† (95% CI)	Median latency (y)‡	No.	SIR (95% CI)
Second cancers, all§	122	1.22 (1.01-1.45)‖	2.4	83	1.07 (0.85-1.33)
Solid tumors, all¶	101	1.13 (0.92-1.38)	2.4	71	1.03 (0.81-1.30)
Salivary gland	3	11.55 (2.32-33.76)‖	0.8	1	4.96 (0.06-27.62)
Stomach	3	1.34 (0.27-3.93)	2.4	2	1.16 (0.13-4.20)
Small intestine	2	6.02 (0.68-21.73)	1.9	1	3.87 (0.05-21.55)
Colon	13	1.23 (0.66-2.11)	3.9	12	1.48 (0.76-2.58)
Rectum**	3	0.88 (0.18-2.58)	2.2	2	0.77 (0.09-2.77)
Other biliary††	3	7.24 (1.46-21.16)‖	3.3	3	9.34 (1.88-27.28)‖
Lung	19	1.28 (0.77-2.01)	2.3	13	1.14 (0.61-1.95)
Skin, malignant melanoma	4	1.45 (0.39-3.71)	2.4	3	1.39 (0.28-4.07)
Female breast	7	0.77 (0.31-1.58)	2.5	6	0.83 (0.30-1.81)
Female genital tract	6	1.67 (0.61-3.64)	4.5	5	1.76 (0.57-4.12)
Male genital tract	14	0.66 (0.36-1.10)	1.1	7	0.43 (0.17-0.89)‖
Bladder	7	1.11 (0.44-2.28)	4.2	6	1.23 (0.45-2.69)
Kidney	3	1.52 (0.31-4.44)	1.1	2	1.15 (0.13-4.17)
Brain	3	3.49 (0.70-10.19)	1.9	2	3.01 (0.34-10.87)
Lymphohematopoietic, all	14	1.70 (0.93-2.86)	2.0	7	1.10 (0.44-2.27)
NHL	10	2.56 (1.23-4.71)‖	2.0	5	1.65 (0.53-3.85)
Multiple myeloma	1	0.76 (0.01-4.25)	5.9	1	0.99 (0.01-5.49)
CLL	3	2.72 (0.55-7.94)	0.5	1	1.18 (0.02-6.56)

NOTE: Cancer sites presented in the table are those for which two or more subsequent cancers were observed after MCC (with the exception of multiple myeloma). Squamous and basal cell carcinomas of the skin are not reportable to the SEER Program, except for genital sites, and thus, are not included in the analyses.

*Risk excludes all cancers occurring within 1 year of a primary MCC diagnosis.

†Risk excludes eight cancers occurring within 1 month of a first primary MCC diagnosis [lung (n = 3), Kaposi sarcoma (n = 1), NHL (n = 1), malignant melanoma (n = 1), small intestine (n = 1), and multiple myeloma (n = 1)].

‡Median time from diagnosis of first primary MCC to diagnosis of second cancer.

§Includes all malignant cancers except MCC. Includes five patients with third or higher order cancers [appendix (n = 1), brain (n = 1), breast (n = 1), prostate (n = 1), and colon (n = 1)].

‖$P < 0.05$.

¶Excludes lymphohematopoietic malignancies (n = 14) and tumors classified as miscellaneous (n = 7).

**Numbers include rectum and rectosigmoid junction.

††Includes all biliary sites other than liver and gallbladder.

O = 3; P = 0.002), biliary sites other than liver and gallbladder (SIR, 7.24; 95% CI, 1.46-21.16; O = 3; P = 0.009), and NHL (SIR, 2.56; 95% CI, 1.23-4.71; O = 10; P = 0.007; Table 2). Nonsignificantly increased risks of 2-fold or higher were seen for CLL, and cancers of the small intestine and brain. Overall, 14 subsequent cancers [median latency, 1.6 years (range, 0.1-10.7 years)] had a histology similar to MCC: neuroendocrine (one salivary gland and one stomach), small cell carcinoma (SCC; one salivary gland, one extrahepatic bile duct, seven lung), or carcinoid (one stomach, one small intestine, and one appendix).

A significantly increased 1.36-fold risk of MCC as a subsequent tumor was observed among patients with all other first primary cancers taken together (Table 3). Significant 3- to 7-fold excesses of MCC followed malignant melanoma, NHL, multiple myeloma, and CLL. Nonsignificant 2-fold excesses of MCC were evident following kidney cancer.

The clinical features of patients with MCC who subsequently developed cancer of the salivary gland, biliary sites other than liver and gallbladder, brain, and NHL are described in Table 4. In all three patients with salivary gland carcinomas, MCC had presented in the head region within the preceding 16 months. Three cancers of extrahepatic bile ducts included one advanced-stage SCC. All brain cancers were glial cell in origin, with latencies of 0.1, 1.9, and 4.1 years, respectively. All cases of secondary NHL for which immunophenotype was specified were B cell, with antecedent MCC arising in the head/neck region or in the upper extremities.

Discussion

The current investigation represents the first, large quantitative study to evaluate the reciprocal risks of multiple primary cancers among patients with MCC. New findings include significantly increased risks of subsequent cancers of salivary gland, brain (men), and biliary sites other than liver and gallbladder. In addition, a significant association between multiple myeloma or CLL and secondary MCC was identified, and previous associations with NHL and malignant melanoma were confirmed.

Although MCC is usually cutaneous, a recent case series (8) indicates that MCC may arise in the salivary gland as a neuroendocrine SCC, consistent with observations in our study. Whether excess salivary gland cancers after MCC represent misclassification of metastatic MCC or the same disease process is unknown. All salivary gland cancers in our study were histologically confirmed, but immunohistochemical expression of cytokeratin 20 has been recommended to classify SCC tumors at this site as MCC (8).

The significantly increased risk of brain cancer in men is noteworthy, but is based on small numbers and may represent a chance finding. Nonetheless, the chromosomal abnormality most frequently reported in MCC is a deletion of chromosome 1 (1p36), (9) and chromosome 1p and 19q deletions have recently been linked to human gliomas (10, 11), the subtype observed in our study. Deletions of chromosome 1 have also been reported in association with the development of malignant melanoma and neuroblastoma, suggesting that a tumor suppressor gene may be located in this region (1). The increased risk of MCC after malignant melanoma in our survey confirms a previous study, suggesting an association with sun exposure and possibly immunosuppression (2). Both MCC and malignant melanoma derive from neural crest cells (5).

The three cancers of extrahepatic bile ducts are unusual. The relatively long latencies (3.3. and 3.8 years) associated with the cases of adenocarcinoma minimize the influence of early surveillance bias as an explanation for the excess risk, although these tumors could have been detected during later work-ups for suspected hepatic metastases of MCC (12). Risk factors for

cancers of the extrahepatic bile duct include gallstones, tobacco and alcohol use, reproductive history (women), diet, and a history of ulcerative colitis (13).

Occurrences of MCC following multiple myeloma or NHL have been reported in descriptive studies or case reports, albeit based on small numbers (2-4, 14, 15). We quantify these associations for the first time, documenting statistically significant elevations. Excesses of NHL both before and after MCC suggest the importance of immunologic factors in the etiology of MCC. However, it is important to note that significant excesses of NHL were restricted to the first year after MCC diagnosis, an observation which suggests a possible surveillance bias within the first year. The significant excesses we found for MCC after multiple myeloma, CLL, and NHL are new, and support previous reports (2, 14) which described MCC in association with B cell cancers.

The increased risk of MCC following malignant melanoma but lack of a reciprocal association is consistent with a previous study conducted by Miller and Rabkin (2). These authors reported five malignant melanomas before the diagnosis of MCC and one malignant melanoma after MCC diagnosis. This observation may reflect the advanced age and high fatality associated with MCC resulting in decreased opportunity to develop subsequent primary tumors compared with patients with a first primary malignant melanoma.

Some of the 14 subsequent cancer cases with neuroendocrine, small cell, or carcinoid differentiation may represent misclassified, metastatic MCC. The most common secondary sites of involvement in MCC include the skin, lymph nodes, liver, lung, bone, and brain, (12, 16); however, metastases to the stomach, small intestine, pancreas, and testis have been documented (12). Reports have estimated that ~50% of patients with MCC will experience hematogenous spread and about one-third present with regional node involvement (17). Prommegger et al. (18) recently reported associations between neuroendocrine tumors and second primary malignancies in a series of 96 patients, although no cases of MCC were observed.

Several methodologic issues associated with population-based studies of multiple primary tumors should be considered in interpreting our results. Registry strengths include the large number of available patients, enabling the quantification of site-specific risks, and minimization of the selection bias inherent in hospital or clinical series. Subsequent cancer risk may be underestimated due to patient migration outside SEER Program areas. Furthermore, our findings should be interpreted cautiously, given the small numbers in substrata analysis, which could generate several significant associations by chance alone. Although a priori hypotheses did not exist for cancers of salivary gland, biliary tract, and brain, the associated small P values support the legitimacy of these findings. An additional consideration in interpreting increased risks of secondary MCC may be due to steadily improving case ascertainment (19). Since inclusion of MCC as a reportable cancer to the SEER Program, there may also be increased coding of tumors as MCC that may have previously been described as small cell or neuroendocrine tumors of other sites. It should always be kept in mind that multiple primary cancers can reflect the effect of a myriad of influences, including treatment, host factors, diagnostic surveillance, shared etiologic factors, natural history, common cellular origins, and gene-environment interactions (20). In particular, due to the limited survival and older age at diagnosis of MCC, iatrogenic cancers per se are difficult to assess; the observed excesses within the first year likely reflect heightened surveillance, shared etiologic influences, or other factors.

The bidirectional evaluation of cancers associated with MCC may provide clues especially into shared etiologic factors. For example, cutaneous MCC may be closely related biologically to

Table 3. Site-specific risk of MCC following other first primary cancers in the SEER Program (1986-2002)

Site of first cancer	No. of first cancers	All subsequent MCC			MCC occurring after 1 year*	
		No.	SIR† (95% CI)	Median latency (y)‡	No.	SIR (95% CI)
First cancers, all	2,048,739	221	1.36 (1.19-1.55)§	4	197	1.40 (1.21-1.61)§
Solid tumors, all‖	1,826,262	184	1.20 (1.04-1.39)§	4	164	1.24 (1.05-1.44)§
Salivary gland	5,241	1	2.67 (0.03-14.84)	5.8	1	3.17 (0.04-17.62)
Stomach	39,130	0	[1.41]	—	0	[1.06]
Small intestine	5,946	0	[0.34]	—	0	[0.29]
Colon	161,356	18	1.07 (0.64-1.70)	4.2	18	1.24 (0.74-1.96)
Rectum¶	66,488	4	0.65 (0.18-1.67)	8.7	4	0.76 (0.20-1.94)
Other biliary**	6,118	0	[0.20]	—	0	[0.14]
Lung	254,292	6	0.88 (0.32-1.92)	1.5	3	0.63 (0.13-1.85)
Skin, malignant melanoma	70,604	16	3.05 (1.74-4.95)§	6.8	14	3.04 (1.66-5.09)§
Female breast	321,190	26	1.29 (0.84-1.89)	5.5	25	1.39 (0.90-2.05)
Female genital tract	132,117	10	1.56 (0.75-2.87)	5.7	10	1.77 (0.85-3.25)
Male genital tract††	356,916	71	1.13 (0.88-1.42)	3.4	58	1.04 (0.79-1.34)
Bladder	84,622	12	0.96 (0.50-1.68)	4.9	12	1.10 (0.57-1.92)
Kidney	40,905	6	2.17 (0.79-4.73)	3	6	2.25 (0.82-4.89)
Brain	29,387	0	[0.21]	—	0	[0.12]
Lymphohematopoietic, all	173,994	34	3.84 (2.66-5.37)§	4	30	4.11 (2.78-5.87)§
NHL	81,743	16	3.37 (1.93-5.47)§	4.1	13	3.28 (1.74-5.60)§
Multiple myeloma	23,949	4	3.70 (1.01-9.47)§	3.4	4	4.91 (1.32-12.57)§
CLL	17,315	14	6.89 (3.77-11.57)§	4.1	13	7.43 (3.95-12.71)§

NOTE: Cancer sites presented in the table are those for which two or more subsequent cancers were observed after MCC (with the exception of multiple myeloma; i.e., replicated sites presented in Table 2). Squamous and basal cell carcinomas of the skin are not reportable to the SEER Program, except for genital sites, and thus, are not included in the analyses. For sites with zero observed cases, the expected number of cases is denoted in brackets [n].

*Risk excludes all cancers occurring within 1 year of a primary MCC diagnosis.

†Risk excludes nine MCC occurring within 1 month of another first primary cancer diagnosis [lung (n = 3), prostate (n = 2), melanoma (n = 2), NHL (n = 1), and larynx (n = 1)].

‡Median time from diagnosis of first cancer to diagnosis of MCC.

§$P < 0.05$.

‖Excludes lymphohematopoietic malignancies (n = 34) and tumors classified as miscellaneous (n = 3).

¶Numbers include rectum and rectosigmoid junction.

**Includes all biliary sites other than liver and gallbladder.

††Includes the development of MCC as a second cancer in 70 men with prostate cancer and one with testis cancer.

Table 4. Characteristics of patients who developed selected subsequent primary cancers after MCC

Case	MCC				Latency (y)	Subsequent cancer		
	Age (y)/ gender	Site	Stage	Initial therapy for MCC		Histology	Site*	Stage
Salivary gland cancer after MCC								
1	77/F	Face	Localized	Surgery only	0.5	Mucoepidermoid tumor	Sublingual gland	Localized
2	91/F	Face	Localized	Surgery only	1.3	Small cell carcinoma	Submandibular gland	Distant
3	84/M	Scalp/neck	Localized	No treatment	0.8	Neuroendocrine carcinoma	Parotid gland	Localized
Cancers of biliary sites other than liver and gallbladder after MCC								
1	85/M	Trunk	Localized	Surgery only	3.3	Adenocarcinoma, NOS	Extrahepatic bile duct	Unknown
2	66/M	Trunk	Localized	Surg/rad/chemo	3.8	Adenocarcinoma, NOS	Extrahepatic bile duct	Regional
3	57/M	Face	Localized	Surgery only	1.8	Small cell carcinoma	Extrahepatic bile duct	Distant
Brain cancer after MCC								
1	68/M	Trunk	Localized	Surgery only	0.1	Glioma, malignant	Frontal lobe	Unknown
2	61/M	Skin, NOS	Regional	Rad/chemo	1.9	Astrocytoma, NOS	Overlapping lesion of brain	Unknown
3	73/M	Face	Unstaged	Surg/rad	4.1	Glioblastoma, NOS	Parietal lobe	Unknown
NHL after MCC								
1	67/M	Scalp/neck	Localized	Surg/rad	0.2	Small B cell lymphocytic	Head/neck	Localized
2	74/M	Face	Unstaged	Surg/rad	0.3	Small B cell lymphocytic	Head/neck	Unknown
3	73/F	Upper limb/ shoulder	Regional	Surgery only	4.3	Small B cell lymphocytic	Multiple regions	Distant
4	59/M	Upper limb/ shoulder	Distant	Surg/chemo	0.1	Small B cell lymphocytic	LN, NOS	Distant
5	77/F	Upper limb/ shoulder	Unstaged	Surgery only	7.1	B cell, follicular	Axilla/arm	Localized
6	70/F	Face	Regional	Surg/rad	3.4	Large B cell, diffuse	Orbit	Distant
7	77/M	Face	Localized	Surgery only	0.6	Large B cell, diffuse	Inguinal region/leg	Localized
8	85/F	Upper limb/ shoulder	Regional	Surg/rad	3.3	NHL, NOS	Jejunum	Regional
9	84/M	Upper limb/ shoulder	Localized	Surgery only	0.9	NHL, NOS	Axilla/arm	Localized
10	86/F	Face	Localized	Surgery only	3.0	NHL, NOS	LN, NOS	Unknown

Abbreviations: NOS, not otherwise specified; LN, lymph node; surg, surgery; rad, radiotherapy; chemo, chemotherapy; M, male; F, female.
*All cases of NHL were diagnosed in lymph nodes, except for one case in the orbit and one in the jejunum.

other small cell and neuroendocrine tumors, as shown for the salivary gland (8). Future analytic investigations should clarify the role of various factors (20), as summarized above in the genesis of multiple primary cancers associated with MCC.

Acknowledgments

We are indebted to Jeremy Miller (Information Management Services, Rockville, MD) for expert computer support and data management.

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